REMARKS

The Specification has been amended to correct a couple of typographical/proofreading errors.

At page 5, lines 17-22 of the instant specification, the citation to the Uemura et al. 1997 article is incorrect. The citation should read "J. Urol. **157**(4 Suppl.)," and not "J. Urol. 154(4 Suppl.)."

The correction at page 26, line 14 of Table 1 changes the Genomic Position of Exon 10 from "10350-70431" to "10350-10431". That error is an obvious typographical/proofreading error in that SEQ ID NO: 37 contains 82 base pairs, and further in view of the context of Exon 10, for example, in light of Intron 10's genomic position which begins at nucleotide 10432 as shown in last line of Table 1.

This response amends Claims 31, 34, 35, 36, 38, and 39 and cancels Claim 40 to point out with more particularlity and clarity the subject matter regarded by the Applicants as their invention. Claim 40 is cancelled due to its being accidentally a duplicate of Claim 39.

Claim 31, the only presently pending independent claim, has been amended to specify with more clarity and particularity the nature of the binding site on the MN protein to which vertebrate cells adhere in a cell adhesion assay. The specification clearly indicates that the M75 monoclonal antibody

("MAb M75") binds specifically to MN proteins/polypeptides. Support for MAb M75 specifically binding MN proteins/polypeptide can be found throughout the Specification, for example, at least at page 2, lines 15-21, which reads:

> Zavada et al, WO 93/18152 and WO 95/34650 describe the production of MN-specific antibodies. A representative and preferred MN-specific antibody, the monoclonal antibody M75 (Mab M75), was deposited at the American Type Culture Collection (ATCC) in Manassus, VA (USA) under ATCC Number HB 11128. The M75 antibody was used to discover and identify the MN protein and can be used to identify readily **MN antigen** in Western blots, in radioimmunoassays and immunohistochemically. . . .

[Emphasis added.] The Specification defines "MN antigen . . . to encompass MN proteins and/or polypeptides." [Specification, page 45, lines 11-12.]

The Specification further clearly supports that the site on the MN protein to which the MN-specific MAb M75 specifically binds is closely related to the MN protein's cell adhesion site. The following passages from the Specification support the use of the MAb M75 to identify MN proteins/polypeptides, and the close association of the site on the MN protein to which the MAb M75 specifically binds with the MN protein's cell adhesion:

> Identified herein is the location of the MN protein binding site. Of particular importance is the region within the proteoglycan-like domain, aa 61-96 (SEQ ID

> NO: 97) which contains a 6-fold tandem repeat of 6 amino acids, and within which the epitope for the M75 MAb resides in at least two copies, and within which the MN binding site is considered to be located.

[Specification, page 5, lines 26-30.]

> A preferred MN binding site is considered to be closely related or identical to the epitope for MAb M75, which is located in at least 2 copies within the 6-fold tandem repeat of 6 amino acids [aa 61-96 (SEQ ID NO: 97)] in the proteoglycan-like domain of the MN protein.

[Specification, page 21, lines 4-7.]

> Treatment of the dots of immobilized MN/CA IX with MAb M75 abrogated its capacity to attach the cells, but the control MAb M16, irrelevant for MN/CA IX had no effect. Blocking of cell attachment by M75 shows that the epitope is identical to or overlapping with the binding site of MN/CA IX for cell receptors.

[Specification, page 66, lines 1-4.]

> There can be no doubt on the specificity of cell attachment to purified MN/CA IX+. It is abrogated by specific MAb M75, at a dilution 1:1000 of ascites fluid.

[Specification, page 69, lines 8-9.]

Claim 31 has been amended to specify that the MN protein or MN polypeptide used in the cell adhesion assay "is specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128. . . ."

The Specification identifies the Budapest Treaty deposit of the VU-M75 hybridoma at the ATCC at least at page 74, lines 1-16.

Claim 31 has also been amended to specify that a MN protein "or a MN polypeptide" can be used in the cell adhesion assay as long as "said MN protein or said MN polypeptide is specifically bound by the M75 monoclonal antibody . . ." and "is encoded by a nucleic acid whose nucleotide sequence is selected from the group . . ." set forth in sections (1), (2) and (3) of Claim 31. The Specification at page 44, lines 19-22 states:

> A "polypeptide" or "peptide" is a chain of amino acids covalently bound by peptide linkages and is herein considered to be composed of 50 or less amino acids. A "protein" is herein defined to be a polypeptide composed of more than 50 amino acids. The term polypeptide encompasses the terms peptide and oligopeptide.

One of skill in the art would know from reading the Specification, as exemplified by the above quoted passages on the close relation of the site on the MN protein to which MAb M75 specifically binds and the MN protein's cell adhesion site, that a MN protein or a MN polypeptide specifically bound by the MAb M75 would be expected to comprise the cell adhesion binding site, and to be effective in the claimed cell adhesion assays.

Claim 31 has further been amended for grammatical clarity and particularity. To correct a proofreading error or inadvertent oversight, "molecules" was changed to "**molecule**" in

line 5, section (c) and section (e) of Claim 31. One of skill in the art would know that one can test organic and/or inorganic molecules individually, sequentially and/or simultaneously in conventional assay format variations of the claimed cell adhesion assays.

In section (a) of Claim 31, "**substrate**" was added after "to which" for antecedent clarity, and "**vertebrate**" was added to modify "cells" for particularity. In section (c) of Claim 31, "said" was changed to "**the**" for specificity, since section (b) refers to "unbound MN protein or unbound MN polypeptide". In section (d) of Claim 31 "**bound**" is added to modify MN protein or MN polypeptide for particularity and clarity.

Claim 34 was amended to correct a proofreading error by adding a period at its end.

Claims 35 and 36 have been amended by deleting SEQ ID NOS: 107, 108 and 109 to correct an accidental oversight. SEQ ID NOS: 107, 108 and 109 are heptapeptides that were not identified by the claimed cell adhesion assays. As explained in Example 3, those heptapeptides bind to the carbonic anhydrase (CA) domain of the MN protein and were identified by a different kind of assay.[2]

---

2. Example 3 at page 70, line 16 to page 71, line 21 of the

Claim 36 has also been amended to correct its dependency to avoid antecedent ambiguity.

Claim 38 has been amended to correct an oversight by deleting "or within the carbonic anhydrase domain of the MN protein." As indicated above, the MN cell adhesion site is considered to be closely associated with or to reside within the proteoglycan-like domain [SEQ ID NO: 50 at amino acids 53-111 of Figure 1] of the MN protein, and not with or within the carbonic anhydrase (CA) domain [SEQ ID NO: 51 at amino acids 135-391 of Figure 1]. As indicated in footnote 1, an assay other than the claimed cell adhesion assay can be used to identify molecules that bind to the CA domain.

Applicants respectfully submit that no new matter has been entered by the above amendments to the pending claims, and respectfully request entry of the above amendments and reconsideration of the application as amended.

Specification discloses methods of identifying peptides binding to MN protein using oligopeptide phage display libraries. In such a method, phage encoding the peptides are incubated with plates coated with MN protein. Unbound phage is washed away, the bound phage is eluted, amplified, eluted by acetazolamide, amplified and used for additional rounds of screening. The fact that phages bearing the SEQ ID NOS: 107, 108 and 109 heptapeptides "were eluted by acetazolamide, an inhibitor of carbonic anhydrase activity, indicates that the peptides bind to the CA domain of MN protein." [Specification, page 71, lines 14-16.] The SEQ ID NOS: 107, 108 and 109 heptapeptides are considered to bind to the enzymatic center of the carbonic anhydrase (CA)

35 U.S.C. Section 112, First Paragraph Rejection

Claims 31-42 stand rejected under 35 U.S.C. Section 112, first paragraph, as "lacking proper written description. . . . [T]he claims are drawn to a genus of nucleotide sequences, and the specification has only defined or disclosed a single species of the broad genus claimed, namely SEQ ID NO: 1." [Office Action, pages 2-3, section 4.]

The Office Action dated May 17, 2004 directs the Applicants' attention to Example 9 of the Revised Interim Written Description Guidelines, in which the written description requirement is satisfied "[b]ecause the specification defines a specific functional activity, and because one of skill in the art would not predict much variability between the hybridizing sequences (due to the strict or stringent hybridization language in the claims). . . ." Applicants respectfully maintain that the claims prior to the instant amendments had met the written description requirement of 35 USC § 112, first paragraph, in view of the definitions of MN proteins/polypeptides and nucleotide sequences, Figures 1-8, as well as SEQ ID NOS: 1-143, among other identifying characteristics for nucleotide sequences encoding MN proteins/polypeptides. However, Applicants further respectfully but emphatically submit that

---

domain of the MN protein and would be considered thereby to inhibit MN's carbonic anhydrase activity.

there can be no question that the claims as amended for particularity and clarity directly present a "specific functional activity" to which the Examiner refers.

Independent Claim 31, from which all the remaining pending claims depend, has been amended for particularity and clarity to indicate that the MN protein or MN polypeptide used in the claimed cell adhesion assays "is specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128. . . . " The genus of nucleotide sequences that hybridize to SEQ ID NO: 1 under stringent hybridization conditions of Claim 31, are then those that encode such MN proteins/polypeptides that are specifically bound by the MAb M75.

The Office Action at the bottom of page 3 admits that "one of skill in the art would recognize a sequence which is 80-90% homologous to that of SEQ ID NO: 1," but states that "the claims do not teach a readily screenable assay for which a specific function can be correlated to a specific structure." Applicants respectfully respond that the claims as amended for particularity and clarity do provide such "a readily screenable assay for which a specific function can be correlated to a specific structure." If a nucleotide sequence hybridizes to SEQ ID NO: 1 under stringent hybridization conditions, that is, if

said nucleotide sequence has a structure that is 80-90% homologous to SEQ ID NO: 1, and if said nucleotide sequence encodes a MN protein or a MN polypeptide that is specifically bound by MAb M75, then one of skill in the art would know that said nucleotide sequence belongs within the genus of nucleotide sequences set forth in Claim 31, section (2). One of skill in the art then does have a screenable assay to determine whether a nucleotide sequence belongs in the genus of nucleotide sequences of Claim 31, section (2); one of skill in the art can test by conventional methods whether the MN protein or MN polypeptide encoded by said nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 is specifically bound by MAb M75, which is secreted by the VU-M75 hybridoma deposited at the American Type Culture Collection.

Then, in Claim 31, the addition of the limitation of:

> wherein said MN protein or said MN polypeptide is specifically bound by the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128, . . .

addresses the Examiner's concerns for "a readily screenable assay . . . for which a specific function can be correlated to a specific structure," that is, to determine whether a sequence that hybridizes specifically under stringent hybridization conditions to the complement of SEQ ID NO: 1, encodes an MN

protein/polypeptide comprising a cell adhesion site [page 3, Final Office Action of May 17, 2004].

Applicants respectfully remind the Examiner that the M75 monoclonal antibody (M75 Mab), the primary subject of the above amendment to claim 31, appeared frequently in the earlier prosecution of the subject application. Applicants respectfully submit that the structure and binding properties of the M75 Mab being a subject of the earlier prosecution of the instant application, should not require further search and new considerations under 35 USC 112, 102 and/or 103.

In the first Office Action of February 12, 2003 at page 4, the Examiner rejected the claims under 35 USC §102(b) as being anticipitated by Zavada et al. [Int. J. Oncology 1997, 10(4):857-863], which described the M75 Mab, because "Zavada *et al* teach the identification of an antibody to MN protein which is used to inhibit the binding of human derived cells in a cell adhesion assay. The antibody identified corresponds to an epitope that is located either in the proteoglycan domain or in the carbonic anhydrase domain." Applicants overcame that argument by showing how in the cited Zavada et al. reference, "[b]locking of adsorbed MN protein with an excess of Mab M75 did not abrogate the adhesion of NIH3T3 cells," but required preliminary incubation with SAC cells. It was not until a later reference that the specific binding of the M75 MAb to the MN

cell adhesion site was demonstrated. That argument was accepted by the Examiner in the second Office Action of September 10, 2003 at page 7.

Also in the second Office Action, the Examiner based a 35 USC § 112, first paragraph rejection (at page 5) on the grounds that "[t]he art teaches that not all antibodies directed against the MN protein are capable of inhibiting the adhesion of MN protein to cells. One such example is Zavada et al (cited previously) wherein it is disclosed that an antibody directed against the MN protein was unable to inhibit the binding of NIH3T3 cells to the MN protein, and only effective upon pre-incubation with SAC." The Applicants responded by pointing out that the instant Specification teaches at page 69, lines 8-13:

> There can be no doubt on the specificity of cell attachment to purified MN/CA IX+. It is abrogated by specific MAb M75, at a dilution 1:1000 of ascites fluid. This is a correction to our previous report in Zavada et al., Int. J. Oncol., 10: 857 (1997) in which we observed that MN/CA IX produced by vaccinia virus vector and fusion protein GST-MN support cell adhesion, but we did not realize that GST anchor itself contains another binding site, which is not blocked by M75.

[Emphasis added.] The Applicants concluded that "the Specification describes a working example, the M75 Mab to the MN protein, which blocks the cell binding site of the MN protein." The Office Action of May 17, 2004 at page 4 indicated that that

35 USC §112, first paragraph rejection was "withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 1/9/2004."

Applicants respectfully conclude that the amendment to claim 31 involving the MN-specific M75 mab squarely meets the instant 112, first paragraph rejection by providing "a readily screenable assay for which a specific function can be correlated to a specific structure." [Office Action of May 17, 2004, page 3.] Applicants respectfully again remind the Examiner that the binding properties of the MN-specific M75 monoclonal antibody have been a subject in earlier prosecution of the instant application, and that the M75 Mab has been previously accepted by the Examiner as a working example of a molecule that blocks the cell binding site of the MN protein, as reflected in the Examiner's statements in the Office Action of May 17, 2004.

Applicants respectfully request that the Examiner reconsider the instant rejection in view of the amendments to Claims 31, 34, 35, 36, 38, and 39 for particularity and clarity and the above remarks, and withdraw the rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claim amendment be entered and that the claims be

promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,

Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

Dated: October 11, 2004